Eosinophilic Gastroenteritis: Using Presenting Findings to Predict Disease Course

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INTRODUCTION: **Studies on eosinophilic gastroenteritis have identified broad spectrums of disease. We aimed to characterize subtypes of disease and ascertain outcomes of each group.**

METHODS: **This is a retrospective cohort study from a large tertiary medical center including 35 patients diagnosed with eosinophilic gastroenteritis from 2007 to 2018. We defined 2 groups of patients based on clinical and laboratory findings at presentation. Severe disease was defined as having weight loss at time of presentation, hypoalbuminemia at presentation, serosal disease involvement, or anemia at diagnosis. The remaining patients were labeled as mild disease group. We collected and compared demographic data, clinical features, laboratory findings, an allergy history, and disease course of both cohorts.**

RESULTS: **Among 35 patients with eosinophilic gastroenteritis, 18 patients met the criteria for severe disease and 17 patients for mild disease. Of the patients with severe eosinophilic gastroenteritis, 6 (38%) had remission without chronic symptoms, whereas 10 (63%) had chronic symptoms requiring chronic medical therapy. Of the mild group, 12 patients (80%) had disease remission without chronic medications. An allergy history was more common in the severe disease group (83%) compared with the mild disease group (45%). Prednisone and open capsule budesonide were the most commonly used treatment medications in both groups.**

DISCUSSION: **Patients with eosinophilic gastroenteritis may be characterized into 2 forms. Patients with weight loss at time of presentation, hypoalbuminemia at presentation, serosal disease involvement, or anemia at diagnosis were associated with a chronic disease course requiring chronic medications.**

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INTRODUCTION

Eosinophilic gastroenteritis, defined by eosinophilic infiltration of the gastrointestinal (GI) tract with the presence of GI symptoms (1), is a rare condition with an estimated prevalence of 5.1 in 100,000 persons (2). Typical presenting symptoms include abdominal pain, nausea, vomiting, diarrhea, and weight loss (3). Eosinophilic gastroenteritis remains a challenging diagnosis for clinicians as up to 20 eosinophils may be present in the normal adult duodenum (4,5), and secondary causes of reactive eosinophilia must be ruled out before the diagnosis can be made (5). A recent randomized controlled trial for eosinophilic gastroenteritis used a cutoff of 30 eosinophils per high-power field (6), although multiple other studies have used >20 eosinophils as the diagnostic criteria (7,8), highlighting variability in diagnostic criteria for the disease. Over the years, studies have attempted to further classify eosinophilic gastroenteritis to guide clinical decision making and elucidate a patient's long-term outcome. In 1970, Klein et al. (9) published a case series of 7 patients using histologic criteria to classify patients based on depth of eosinophil infiltration. The Klein classification defined 3 separate levels of disease as mucosal disease, muscularis disease, and serosal level disease. Since its publication, the Klein classification has been widely used to define patient groups in studies on eosinophilic gastroenteritis.

Although the Klein classification is based on histological definitions of disease, a recent study with a mean follow-up of 13 years determined 3 clinical courses of eosinophilic gastroenteritis (8). In this study, some patients had a single flare, others had recurrent flares requiring intermittent medications, and a final group had a continuous, chronic course. Of interest, histologic level as defined by the Klein classification (mucosal, muscularis, or serosal involvement) did not correlate well with the clinical courses observed. Given the utility in prediction of clinical courses in patient counseling and treatment planning, we sought to determine what factors at diagnosis could be used to predict course of disease. Factors were chosen based on known associations with other diseases. Anemia and weight loss are considered alarm features in GI diseases, leading us to postulate they

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would be associated with a more severe disease phenotype. Hypoalbuminemia was chosen because low albumin has been associated with malnutrition and protein losing enteropathy and has been demonstrated to have a predictive value on morbidity in various disease states (10). Serosal disease involvement was chosen on the basis that full thickness involvement leading to eosinophilic ascites indicates a more robust tissue response that would likely be correlated with a more chronic, severe disease course. With this reasoning, we hypothesized that the chronic disease courses requiring chronic medications would also have a more severe presentation with anemia at diagnosis, hypoalbuminemia at diagnosis, weight loss at diagnosis, or serosal level of disease at presentation. Thus, we aimed to further describe this rare disease and to evaluate our new classification in its ability to predict disease course.

METHODS

This study was a retrospective chart review including patients seen at Mayo Clinic Rochester and Mayo Clinic Florida. The study was reviewed and received approval from the Mayo Clinic international review board. The advanced cohort explorer tool was used to search the International Classification of Diseases, Tenth Revision, Clinical Modification, the International Classification of Diseases, Ninth Revision, Clinical Modification, and Hospital International Classification of Disease diagnostic codes for eosinophilic gastroenteritis, eosinophilic gastritis, eosinophilic gastroenteritis and colitis, and eosinophilic colitis with diagnostic dates falling between January 1, 2007, and December 31, 2008. Given the rarity of these diseases, the sample size of the study was determined by the number of cases available for review during the given timeframe. The initial search revealed 232 unique patients. Each patient was reviewed for a diagnosis of eosinophilic gastroenteritis. Patients were included if the reading pathologist noted eosinophilia on GI tract biopsy or if there was evidence of eosinophilic ascites. The patient also had to carry a diagnosis of eosinophilic gastroenteritis within clinical notes. Exclusion criteria included evidence of parasitic infection, inflammatory bowel disease, connective tissue disease, vasculitis, amyloidosis, hypereosinophilic syndrome, any malignancy, involvement in a clinical trial, or lack of GI follow-up visit. After application of the exclusion criteria, 35 cases remained for the study.

After ascertainment of cases, the following data were collected: age at diagnosis, sex, ethnicity, body mass index, presenting symptoms, anemia at diagnosis, serum immunoglobulin E levels, albumin level at diagnosis, peripheral eosinophil count at diagnosis, food allergy, types of allergy history, course of disease, and treatment given by the patient's provider. Patients were classified by the Klein classification using the methods specified in their study (9). Hypoalbuminemia was defined by our reference standard of less than 3.5 g/dL, with anemia defined as hemoglobin of less than 13.2 g/dL. Weight loss at presentation was defined by either a patient identified unintentional weight loss or documented weight loss of greater than 5 lbs. All data were collected from the medical chart and placed into a spreadsheet for further analysis. The cohort was then split into 2 groups based on presenting features. One group was defined as severe disease based on the presence of any of the following characteristics: weight loss at the time of presentation, hypoalbuminemia at presentation, serosal disease involvement, or anemia at diagnosis. Patients not having any of these criteria were classified as mild disease group.

Descriptive statistics on patient demographics and clinical characteristics are presented as mean with SD or count (percentage) as appropriate. Because some variables could not be collected, percentages were calculated on the basis of the collected denominators available. To test the difference between the mild form and severe form of eosinophilic gastroenteritis, each variable was compared using the Fisher exact test. A 2-tailed alpha level of 0.05 for each variable examined was used to assess statistical significance. All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Cary, NC).

RESULTS

We identified 35 patients with eosinophilic gastroenteritis; 18 met our criteria for severe disease and 17 for mild disease. The average follow-up time for individuals in the cohort was 5.3 years. Esophagogastroduodenoscopy or colonoscopy was the diagnostic test in 33 of 35 patients, with 2 patients having full-thickness surgical biopsies and 5 having ascitic fluid available for analysis. By the Klein classification, 30 patients had mucosal disease and 5 serosal disease. One patient presented with bowel obstruction due to a stricture with significant eosinophilic infiltrate, whereas all other patients did not require endoscopic or surgical therapies. Table 1 summarizes the demographic data of each group. Overall, the mean age of diagnosis of the mild form of eosinophilic gastroenteritis was 44.0 and the severe form 43.8, showing no significant difference between the groups. Eighty-two percentage of those with mild disease were women compared with 61% of the severe cohort, which reached statistical significance ($P = 0.05$). The study population was predominately Caucasian, with an average body mass index of 29.8 in the mild form of eosinophilic gastroenteritis and 27.2 in the severe form (no significant difference).

Clinical features of the 2 groups are presented in Tables 2–5. The mean time to diagnosis was 2.5 years in those with mild disease and 1.8 years in those with severe disease, which was not statistically significant ($P = 0.61$). Abdominal pain, nausea/vomiting, and diarrhea were the most common presenting symptoms, representing 74%, 57%, and 54% of cases, respectively. Other less common symptoms included weight loss, dysphagia, and constipation. Of the patients with weight loss, 1 was treated with parenteral nutrition and, after treatment with oral steroids, was able to regain weight appropriately and return to a normal diet. None required treatment with nasogastric tube feeding. There was no statistically significant difference in presenting features between the mild and severe disease cohorts. There was a statistically significant difference in the amount of food allergies, with only 1 patient in the mild form of eosinophilic gastroenteritis having a food allergy and 8 patients in

Table 1. Cohort demographics

	Mild disease (n = 17)	Severe disease (n = 18)	*P* value
Age (mean, SEM) at diagnosis	44.0 ± 4.0	43.8 ± 3.9	0.97
Sex, %			0.05
Men	18	39	
Women	82	61	
Ethnicity, %			0.17
White	88	83	
Others	12	17	
BMI, kg/m^2 (mean ± SEM)	29.8 ± 2.0	27.2 ± 1.9	0.43

BMI, body mass index; SEM, standard error of mean.

Table 2. Presenting symptoms

	Mild disease (n = 17)	Severe disease (n = 18)	*P* value
Abdominal pain, n (%)	15 (88%)	11 (61%)	0.12
Nausea/vomiting, n (%)	11 (65%)	9 (50%)	0.5
Diarrhea, n (%)	8 (46%)	11 (61%)	0.5
Weight loss, n (%)	0	4 (22%)	0.1
Dysphagia, n (%)	1 (6%)	1 (6%)	1
Constipation, n (%)	0	1 (6%)	1

All data obtained from documentation at initial gastroenterology encounter.

the severe eosinophilic gastroenteritis group having food allergies. The allergy history reported by the patients in the severe disease group included 4 with atopy (24%), 7 with asthma (39%), 10 with hay fever (56%), and 5 with rhinitis (28%). Regarding disease course, the mild eosinophilic gastroenteritis group had 12 patients (80%) who had disease remission without chronic medications and only 3 (20%) with chronic symptoms requiring chronic medications. Of the patients with severe eosinophilic gastroenteritis, 6 (38%) had remission without chronic symptoms, whereas 10 (63%) had chronic symptoms requiring chronic medical therapy. Two patients with mild disease and 2 patients with severe disease did not have a follow-up visit after initiation of medication therapy. There was statistical significance ($P = 0.03$) when comparing these 2 groups. Two patients in the severe cohort and 5 in the mild cohort had disease courses with relapses most often treated with steroid therapy, followed by medication-free periods. When separated by need for chronic suppressive medication therapy (Table 4), there was no difference in female sex (11 remissions without chronic medications and 10 chronic symptoms requiring chronic medicines) or symptom duration (1.4 years of remission without chronic medications and 2.2 years of chronic symptoms requiring chronic medications). The mean age of patients not requiring chronic medications was significantly higher than those requiring chronic suppressive medications, with the mean age of 48.6 vs 37.9, respectively ($P = 0.04$). The mean follow-up time for those requiring chronic suppressive medications was 6.0 years. Eight patients with chronic disease requiring chronic medication had a history of food allergy, whereas only 1 patient without a need for chronic medications had a history of food allergy.

Treatment medicines are described in Table 5. Prednisone was used by 14 patients (78%) of the severe disease cohort and by 8 patients (47%) of the mild disease cohort. Open capsule budesonide was used by 11 patients (64%) in the severe disease cohort and by 6 patients (50%) in the mild cohort. Other treatments used were cromolyn, montelukast, antihistamine, prednisone, and dietary modification. Only montelukast use was significantly different between the mild and severe cohorts ($P = 0.02$).

DISCUSSION

In this study, we found that weight loss, hypoalbuminemia, serosal disease involvement, or anemia at diagnosis put the patient at higher risk for having a chronic disease type requiring chronic medication. To our knowledge, using this system of classifying eosinophilic gastroenteritis at diagnosis has not been reported in the literature. We propose using these features at clinical presentation to help set patient expectations, guide decision making, and possibly change approach to therapy.

Notably, our study closely correlated with other studies regarding rates of each clinical disease type. In the study by Chambrun et al., 40% of patients had disease that resolved spontaneously without relapse, whereas 50% had had unpredictable relapses and a chronic course (7). These numbers closely approximate our study where 58% of patients did not require chronic medication for symptom control. Other studies reported rates of intermittent flare type disease not requiring chronic medications to be between 30% and 60% (11–13). Overall, there seems to be a wide spectrum of disease emerging from the literature with 1 group characterized by rare/intermittent flares with treatment only when symptomatic and another requiring chronic suppressive medication.

One question posed by this clinical variability is whether there are different pathophysiologies underlying the currently understood disease spectrum of eosinophilic gastroenteritis. Although there was a significant difference in age between cohorts when stratifying by the need for chronic medication therapy, the 2 oldest patients in the cohort were both a part of the remission without chronic medication group. More notably, the severe disease cohort was more likely to have a history of allergy than the mild disease cohort. There is a trend of documented allergies with relapsing

Table 3. Clinical features

	Mild disease (n = 17)	Severe disease (n = 18)	*P* value
Symptom duration before diagnosis (yr)	2.26	1.88	0.61
Anemia present, n (%)	0 (0%)	8 (44%)	0.004
Serum IgE, U/mL	94.2 ± 41.3	438.0 ± 244.0	0.16
Albumin, g/dL	4.3 ± 0.2	3.4 ± 0.2	0.001
Peripheral eosinophil counts (μL)	1,699.4 ± 440.3	1796.7 ± 427.9	0.31
Elevated peripheral eosinophils, n %	11 (65%)	16 (89%)	0.12
Food allergy, n (%)	1 (13%)	8 (67%)	0.03
Type of allergy history, n (%)	6 (43%)	16 (94%)	0.1
Atopy	0 (0%)	4 (24%)	0.05
Asthma	2 (12%)	7 (39%)	0.12
Nasal polyp	0 (0%)	1 (6%)	1.0
Hay fever	3 (18%)	10 (56%)	0.04
Rhinitis	6 (35%)	5 (28%)	0.73
Follow-up, n (%)[a]			0.03
Remission without chronic medication, n (%)	12 (80%)	6 (38%)	
Chronic symptoms requiring chronic medications, n (%)	3 (20%)	10 (63%)	

EGE, eosinophilic gastroenteritis; IgE, immunoglobulin E.
[a]Two patients with mild form and 2 patients with severe form were excluded because no follow-up visit data were available after they began EGE-directed therapy.

Table 4. Associations with need for chronic medication

Finding at diagnosis	Remission without chronic medication	Chronic symptoms requiring chronic medications	*P* value
Female sex	11	10	1
Age (mean)	48.6	37.3	0.04
Symptom duration before diagnosis (yr)	1.4	2.2	0.16
Food allergy	1	8	0.005

disease type in multiple studies (8,12,14) although the studies have had various levels of statistical significance. In particular, a study by Sato et al. (12) found that patients with a single flare without relapse did not have any extra-GI allergic disorders such as asthma, allergic rhinitis, and atopy. They concluded that a single flare may be representative of a nonallergic response and that extra-GI allergies may be associated with chronicity and multiple flares. It is also possible that single flares of disease are one-time reactive processes to a pathogen or other insult that cannot be identified. Regarding the more chronic disease types, there may be parallels to eosinophilic esophagitis where it is possible that food allergy and its contact with the mucosa is the driver for tissue eosinophilia (15) and the chronic disease course may be due to recurrent allergen exposures within the GI tract. Although dietary interventions have been successful in achieving histologic remission in eosinophilic esophagitis (16), a systematic review on dietary elimination therapy in eosinophilic gastroenteritis was unable to find any significant evidence to support dietary elimination therapy (17). In our cohort, elimination diets were only attempted by 2 patients. One found the diet difficult to adhere to, and the other reported no significant benefit and was treated with medical therapy. Overall, although studies show evidence of allergy being associated with the more severe form of eosinophilic gastroenteritis, the available evidence falls short of a causal relationship.

Independent of disease severity, our study found that 77% of patients had an elevated peripheral eosinophil count. Previous studies have documented elevated peripheral eosinophil counts (18,19), with some studies reporting rates up to 86% (20). Although peripheral eosinophilia is not a diagnostic criterion for eosinophilic gastroenteritis, its presence should certainly raise suspicion for the disease. In our study, however, the absolute value of peripheral eosinophilia was not correlated with disease severity, suggesting that it is not a tool to be used in stratifying between those at risk for chronic disease.

Regarding treatments, prednisone and open capsule budesonide were the most common therapies used in our cohort. Opening the capsule of budesonide allows for targeting of the proximal GI tract as opposed to the traditionally taken whole pill that targets the terminal ileum. In many cases of worsening disease on budesonide, systemic corticosteroids were the next recommended step. Unfortunately, objective data such as repeat biopsies were often unavailable for review in our cohort. However, studies have suggested that treatment with budesonide is safe and effective, with 1 recent study showing that it had a similar effect to prednisone in children (21). Our recommendation is to use this agent first line, particularly in patients with severe forms of disease. Of interest, more than half of patients with eosinophilic gastroenteritis were treated with either topical or systemic steroids, indicating this was the most commonly used treatment in our referral center. We would also recommend this treatment for recurring or relapsing disease. There are also 2 emerging treatments worthy of mention, although neither was used by patients in our cohort. The first, vedolizumab, was studied in a set of steroid refractory patients and shown to have a clinical and histological improvement rate of 75% (13). Another recently emerging treatment is anti-siglec-8 antibodies, which have been shown to significantly reduce GI eosinophils and symptoms (20). Despite promising new treatment options for eosinophilic gastroenteritis, future studies are needed in this area.

There are multiple limitations to this study. Eosinophilic gastroenteritis is a rare condition, and this study represents retrospective analysis of only 35 patients. However, this is in line with the number of patients in recently published studies (7,20). Given the limited number of patients, subgroup analysis of each individual clinical feature and its association with a disease course requiring chronic medications was insufficient to properly evaluate for statistical significance. In addition, as a tertiary medical center, there is likely referral bias in our population, and it is possible that diagnoses made in the community setting would be more likely to fall into the mild category. Despite these limitations, we think the study has good external reliability because more severe presenting features such as weight loss at time of presentation, hypoalbuminemia at presentation, serosal disease involvement, or anemia at diagnosis should portend a more chronic disease course in varied populations. In addition, although there was a statistically significant difference between the disease courses of our mild and severe disease groups, there were still one-third of patients in the severe disease category who did not develop a chronic course requiring chronic medication therapy. Finally, the need for chronic drug therapy was defined by clinical symptoms, and we were unable to determine objective efficacy of therapy because repeat biopsies were not available on a large percentage of the cohort.

In conclusion, we defined 2 groups of patients with eosinophilic gastroenteritis based on their clinical presentation and laboratory data. Weight loss, hypoalbuminemia, serosal disease involvement, anemia at diagnosis, or a history of food allergies was associated with a chronic disease course requiring chronic medications. Patients without any of the abovementioned criteria at presentation often had a disease course defined by flares and remissions or a single episode without reoccurrence. Utilization of this classification criteria will help practitioners discuss the different disease courses of eosinophilic gastroenteritis and can help determine the likelihood a patient will require chronic medical therapy.

Table 5. Treatment medications

	Mild form (n = 17)	Severe form (n = 18)	*P* value
Prednisone	8	14	0.09
Budesonide	6	11	0.18
Cromolyn	2	5	0.42
Montelukast	1	8	0.02
Antihistamine	2	3	1
Dietary modification	7	9	0.74

CONFLICTS OF INTEREST

Guarantor of the article: Joseph A. Murray, MD.

Specific author contributions: J.A.M.: overall study supervision by principal investigator. J.A.M, R.S.C., and D.H.: study concept and design, analysis, and interpretation of data. D.H.: acquisition of data and drafting of the manuscript. J.A.M. and R.S.C.: critical review and editing of the manuscript. R.S.C.: statistical analysis. There was no funding or significant administrative, technical, or material support for this project. All authors gave final approval of the project and agreed to be accountable for all aspects of the work.

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Study Highlights

WHAT IS KNOWN

- ✓ Eosinophilic gastroenteritis is a rare condition that is defined by eosinophilic infiltration of the gastrointestinal tract with the presence of gastrointestinal symptoms.
- ✓ Variable disease courses have been described, from severe disease requiring chronic suppressive medications to single flares without reoccurrence.
- ✓ No criteria at diagnosis have been described to help predict disease course.

WHAT IS NEW HERE

- ✓ Patients with weight loss at time of presentation, hypoalbuminemia at presentation, serosal disease involvement, or anemia at diagnosis predicted patients who were more likely to have a chronic disease course requiring chronic medications.

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